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(54) Controlled release-initiation and controlled release-rate pharmaceutical composition
Arzneimittel mit gesteuertem Beginn und gesteuerter Rate der Freisetzung
Composition pharmaceutique avec commencement et vitesse contrôlés de la libération

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(73) Proprietor: SS PHARMACEUTICAL CO., LTD.
Chuo-ku, Tokyo 103 (JP)

(72) Inventors:
• Okada, Minoru
Inba-gun, Chiba (JP)
• Ono, Kenji
Sakura-shi, Chiba (JP)
• Kasai, Shuichi
Narita-shi, Chiba (JP)
• Iwasa, Akira
Yotsukaidoh-shi, Chiba (JP)

(74) Representative:
Hansen, Bernd, Dr. Dipl.-Chem. et al
Hoffmann Eitle,
Patent- und Rechtsanwälte,
Arabellastrasse 4
81925 München (DE)

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Description

FIELD OF THE INVENTION

[0001] This invention relates to a controlled release-initiation and controlled release-rate pharmaceutical composition in which the starting time of the release of a drug from a preparation and the releasing rate of the drug after commencement of its release can be controlled at will.

BACKGROUND OF THE INVENTION

[0002] When a pharmaceutical composition is applied to patients, it is necessary to guarantee its efficacy and safety, as well as its specificity corresponding to each purpose.

[0003] Because of this, great concern has been directed toward the development of a system in which a pharmaceutical composition is designed in such a dosage form that a drug of interest is delivered to a target site for a necessary period of time in a required amount.

[0004] In order to satisfy such a requirement, sustained release preparations which can give prolonged duration of action of a drug by controlling the releasing rate of the drug from the preparation have already been developed and put into practical use. Documents US-A-4 859 469, US-A-4 268 496, EP-A-0 519 870, US-A-4 871 549, WO-A-9 309 785 and Chemical abstracts, vol. 111 (18), 1989, no. 160244W disclose pharmaceutical compositions for controlled release comprising a drug containing core and a coating which consists essentially of a water insoluble high polymer and silicone. However the quantitative composition of the coating is different. In addition, other types of pharmaceutical compositions which can control commencement of the release of drugs have been proposed in recent years, such as a preparation in which a drug is released when the coat membrane of the preparation is disrupted due to swelling of a water swelling material (JP-A-62-30709 (corresponding to U.S. Patent 4,871,549) and JP-A-4-338323; the term "JP-A" as used herein means an "unexamined published Japanese patent application"), a preparation in which a water repellent salt such as magnesium stearate, calcium stearate or the like fatty acid metal salt and an acrylic polymer are used in its coat membrane in order to give the preparation a lag time before the release of its ingredients (JP-A-4-235123 (corresponding to U.S. Patent 5,137,733)) and a preparation in which mutual interaction between Eudragit RS (manufactured by Rohm Pharma GMBH) and an organic acid is applied (Abstract of Papers, 7th Annual Meeting of The Japanese Society of Pharmacy, p.84, 1991).

[0005] However, since drugs are produced with various purposes, development of a pharmaceutical composition having various drug release mechanisms which can respond to these purposes has been called for in

the field of medicine.

SUMMARY OF THE INVENTION

[0006] In view of the above, an object of the present invention is to provide a pharmaceutical composition of new construction in which the starting time of the release of a drug from the preparation and the releasing rate of the drugs, after commencement of its release, can be controlled.

[0007] With the aim of overcoming the aforementioned problems involved in conventional compositions, the inventors of the present invention have conducted intensive studies and found that, when a drug-containing composition is coated with a membrane layer comprising a water insoluble high polymer and silicone, the starting time of the release of the drug can be controlled at will by changing the thickness of the membrane, and the releasing rate of the drug after commencement of its release can be controlled by changing the composition of the membrane. The present invention has been accomplished on the basis of these findings.

[0008] Thus, the present invention provides a controlled release-initiation and controlled release-rate pharmaceutical composition in which a drug-containing composition is coated with a membrane layer which contains a water insoluble high polymer and silicone, as further defined in the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0009] Fig. 1 is a graph showing the results of dissolution tests carried out in Test Example 1 using the controlled release-initiation and controlled release-rate pharmaceutical compositions obtained in Example 1 and comparative preparations obtained in Comparative Example 1. In Fig. 1, the curves, -○-, -□-, -●- and -■- stand for the results of Example 1-1, Example 1-2, Comparative Example 1-1 and Comparative Example 1-2, respectively.

[0010] Fig. 2 is a graph showing the results of tests of excretion into urine carried out in Test Example 2 using the controlled release-initiation and controlled release-rate pharmaceutical compositions obtained in Example 2. In Fig. 2, the curves, -○- and -□- stand for the results of Example 2-1 and Example 2-2, respectively.

[0011] Fig. 3 is a graph showing the results of dissolution tests carried out in Test Example 3 using the controlled release-initiation and controlled release-rate pharmaceutical compositions obtained in Example 3. In Fig. 3, the curves, -○-, -□- and -Δ- stand for the results of Example 3-1, Example 3-2 and Example 3-3, respectively.

[0012] Fig. 4 is a graph showing the results of dissolution tests carried out in Test Example 4 using the controlled release-initiation and controlled release-rate pharmaceutical compositions obtained in Example 4. In Fig. 4, the curves, -○-, -□- and -Δ- stand for the results

of Example 4-1, Example 4-2 and Example 4-3, respectively.

[0013] Fig. 5 is a graph showing the results of dissolution tests carried out in Test Example 5 using the controlled release-initiation and controlled release-rate pharmaceutical compositions obtained in Example 5. In Fig. 5, the curves, -○-, -●-, -□- and -■- stand for the results of Example 5-1, Example 5-2, Example 5-3 and Example 5-4, respectively.

[0014] Fig. 6 is a graph showing the results of dissolution tests carried out in Test Example 6 using the controlled release-initiation and controlled release-rate pharmaceutical compositions obtained in Example 6. In Fig. 6, the curves, -○-, -□- and -Δ- stand for the results of Example 6-1, Example 6-2 and Example 6-3, respectively.

[0015] Fig. 7 is a graph showing the results of dissolution tests carried out in Test Example 7 using the controlled release-initiation and controlled release-rate pharmaceutical compositions obtained in Example 7. In Fig. 7, the curves, -○-, -□- and -Δ- stand for the results of Example 7-1, Example 7-2 and Example 7-3, respectively.

[0016] Fig. 8 is a graph showing the results of dissolution tests carried out in Test Example 8 using the controlled release-initiation and controlled release-rate pharmaceutical compositions obtained in Example 8. In Fig. 8, the curves, -○- and -□- stand for the results of Example 8-1 and Example 8-2, respectively.

[0017] Fig. 9 is a graph showing the result of a dissolution test carried out in Test Example 9 using the controlled release-initiation and controlled release-rate pharmaceutical composition obtained in Example 9. In Fig. 9, the curve, -○- stands for the result of Example 9-1.

[0018] Fig. 10 is a graph showing the result of a dissolution test carried out in Test Example 10 using the controlled release-initiation and controlled release-rate pharmaceutical composition obtained in Example 10. In Fig. 10, the curve, -○- stands for the result of Example 10-1.

[0019] Fig. 11 is a graph showing the result of a dissolution test carried out in Test Example 11 using the controlled release-initiation and controlled release-rate pharmaceutical composition obtained in Example 11. In Fig. 11, the curve, -Δ- stands for the result of Example 11-1.

[0020] Fig. 12 is a graph showing the results of dissolution tests carried out in Test Example 12 using the controlled release-initiation and controlled release-rate pharmaceutical compositions obtained in Example 1 and comparative preparations obtained in Comparative Example 2. In Fig. 12, the curves, -○-, -□-, -●- and -▲- stand for the results of Example 1-1, Example 1-2, Comparative Example 2-1 and Comparative Example 2-2, respectively.

[0021] Fig. 13 is a graph showing the results of dissolution tests carried out in Test Example 13 using the controlled release-initiation and controlled release-rate

pharmaceutical compositions obtained in Example 1 and comparative preparations obtained in Comparative Example 3. In Fig. 13, the curves, -○-, -□-, -●- and -▲- stand for the results of Example 1-1, Example 1-2, Comparative Example 3-1 and Comparative Example 3-2, respectively.

DETAILED DESCRIPTION OF THE INVENTION

[0022] In the pharmaceutical composition of the present invention, a composition containing a drug of interest forms the central core of the preparation, which may be used in the crystalline form of the drug as such or as any of the usually used solid dosage forms such as fine granules, granules, beads, tablets and the like, by mixing the drug with pharmaceutically acceptable carrier, such as fillers, binders, lubricants and the like. As occasion demands, the central core composition may be coated with a water soluble high polymer, an acid soluble high polymer, an enteric high polymer, a water insoluble high polymer, wax or the like. Though not particularly limited, typical examples of the drug to be contained in the central core composition include: drugs for use in the treatment of central nervous system related diseases, such as hypnotics, sedatives, antiepileptics, antipyretics, analgesics, antiinflammatory agents, stimulants, antihypnotics, antidiotics, psychoneurosis treating drugs and the like; drugs for use in the treatment of peripheral nervous system related diseases, such as skeletal muscle relaxants, autonomic agents, autonomic blocking agents, preparations containing plant extracts and the like; drugs for use in the treatment of sensory organ related diseases, such as ophthalmic preparations, otorhinologic preparations and the like; drugs for use in the treatment of circulatory organ related diseases, such as cardiotonics, antiarrhythmic agents, diuretics, hypotensive agents, capillary stabilizers, vasoconstrictors, vasodilators, antiarteriosclerosis agents and the like; drugs for use in the treatment of respiratory organ related diseases, such as respiratory stimulants, respiratory depressants, antitussives and the like; drugs for use in the treatment of digestive organ related diseases, such as peptic ulcer treating drugs, stomachics, digestants, antacids, cathartics, cholagogues, intestinal function controlling drugs and the like; hormones, such as hormones and hormone antagonists and the like; drugs for use in the treatment of urogenital organ and anus related diseases, such as urinary antiseptics oxytocics, urogenital drugs, hemorrhoid treating drugs, rectal preparations and the like; metabolic drugs, such as vitamins, aphrodisiacs, drugs for blood and body fluid, drugs for hepatic disease, antidotes, habitual intoxication treating agents, arthrifuges, enzyme preparations, antidiabetic drugs and the like; drugs for use in the treatment of tissue and cell function related diseases, such as cell activation drugs, antimalignant neoplastic agents and the like; drugs for use in the treatment of pathogenic organisms related diseases, such as antibi-

otics, chemotherapeutic agents, antiprotozoan agents, anthelmintics and the like; and narcotics such as alkaloid-type narcotics, non-alkaloid-type narcotics and the like.

[0023] Illustrative examples of the water insoluble high polymer to be used in the membrane layer of the pharmaceutical composition of the present invention include: water insoluble high polymers such as a terpolymer composed of ethyl acrylate, methyl methacrylate and ethyl trimethylammonium chloride methacrylate, ethyl cellulose and the like; and enteric high polymers which are insoluble under acidic condition, such as a copolymer composed of methacrylic acid and ethyl acrylate, a copolymer composed of methacrylic acid and methyl methacrylate, hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose acetate succinate, carboxymethylcellulose, cellulose acetate phthalate and the like. Of these high polymers, the ethyl acrylate/methyl methacrylate/ethyl trimethylammonium chloride methacrylate terpolymer is particularly preferred, because it is most effective in prolonging the duration before drug-releasing while using (lag time) a lesser amount of coating. Preferably, the terpolymer has an ethyl acrylate:methyl methacrylate:ethyl trimethylammonium chloride methacrylate weight ratio of 1:2:0.1 to 1:2:0.2. Its commercially available examples include Eudragit RS and Eudragit RL (manufactured by Rohm Pharma GMBH).

[0024] The water insoluble high polymers exemplified above may be used alone or as a mixture of two or more, preferably in a range of from 20 to 95% by weight based on the total weight of the membrane layer.

[0025] The lag time and drug-releasing rate can be controlled by adding a small amount of a water soluble high polymer to the aforementioned water insoluble high polymer. Preferred examples of the water soluble high polymer include hydroxypropylmethyl cellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone, polyethylene glycol and the like, preferably in a range of from 1 to 4% by weight based on the total weight of the membrane layer.

[0026] A silicone resin or a silicone oil, particularly dimethylpolysiloxane having a viscosity of 95 to 1,100 centistokes, is used preferably as the silicone to be contained in the membrane layer. The silicone is contained in the membrane layer in an amount of at least 5%, preferably from 5 to 200% by weight, more preferably from 10 to 100% by weight, based on the aforementioned water insoluble high polymer.

[0027] It is preferable to add a silicone hold carrier to the membrane layer. Addition of a silicone hold carrier renders possible not only the inclusion of a large amount of silicone in the membrane layer but also the production of a highly stable pharmaceutical composition whose lag time before the release of a drug and the drug-releasing rate thereafter do not change even when a large amount of silicone is included in the membrane layer.

[0028] The silicone hold carrier is not particularly lim-

ited, provided that it can disperse and retain a liquid silicone in the water insoluble high polymer, but is selected preferably from talc, light anhydrous silicic acid, microcrystalline cellulose, starch and the like, of which light anhydrous silicic acid is particularly preferred. Preferably, the silicone hold carrier is used in the form of a fine powder having a large surface area. The silicone hold carrier is used in an amount of preferably from 0 to 200% by weight based on the silicone to be used.

[0029] A plasticizer may be further added to the membrane layer. Examples of useful plasticizers include triethyl citrate, triacetin, polyethylene glycol, castor oil, polyoxysorbitan monooleate, glycerine fatty acid ester and the like, which is preferably used in an amount of from 2 to 50% by weight based on the water insoluble high polymer.

[0030] The membrane layer to be coated is used in an amount of from 25 to 200% by weight based on the central core weight, though it varies depending on the type of drug to be used, size and shape of the central core, intended lag time and release rate and composition of the membrane. In general, it is necessary to increase the coating quantity when a longer lag time is required, and the coating quantity also becomes large when the central core is small.

[0031] The pharmaceutical composition of the present invention can be produced by making central cores in the usual way and then coating each core with a membrane layer which contains a water insoluble high polymer and silicone.

[0032] Central cores can be produced by various known processes, such as a process in which fine granules and granules are produced by wet or dry granulation, a process in which these fine granules and granules are made into tablets by compression molding, a process in which tablets are produced by direct compression tableting, a process in which granules and beads are produced by rotary granulation, a process in which fine granules, granules and beads are produced by extrusion granulation and a process in which granules and beads are produced by extrusion granulation and subsequent treatment with Marumerizer (Fuji Paudal Co., Ltd.) or the like. Coating of the membrane layer may be effected by spray-coating the central cores with the membrane layer composition in a fluidized bed or a pan.

[0033] The controlled release-initiation and controlled release-rate pharmaceutical composition of the present invention may be further combined with an immediate-release preparation or with another inventive controlled release-initiation and controlled release-rate pharmaceutical composition having different lag times.

[0034] The controlled release-initiation and controlled release-rate pharmaceutical composition of the present invention once made into fine granules, granules, beads or tablets may be further made into a capsular dosage form by packing them into capsules, or the inventive fine granules, granules or beads may be made into tablets

together with appropriate fillers, binders, lubricants and the like.

[0035] Since the controlled release-initiation and controlled release-rate pharmaceutical composition of the present invention can start the release of a drug from the preparation after a predetermined lag time, it can be made into sustained release preparations having various drug-releasing patterns by combining it with an immediate-release preparation or other preparations having different lag times. In addition, since the release of a drug can be set to a pulse type, the same blood concentration transition as the case of the administration of an immediate-release preparation several times a day can be obtained by once a day administration of the inventive preparation.

[0036] When a drug to which first-past effect exerts an adverse influence is applied in the form of a conventional sustained-release preparation, bioavailability thereof is extremely reduced. In accordance with the present invention, however, the decrease of bioavailability of such drug can be lessened because the inventive preparation can be set to a pulse type drug release pattern in which a drug of interest is released quickly at predetermined drug release starting times.

EXAMPLES

[0037] The following examples are provided to further illustrate the present invention. The term "%" as used herein means "% by weight".

EXAMPLE 1

[0038] A 1,500 g portion of trapidil was mixed with 100 g of hydroxypropyl cellulose and pulverized into fine powder. While spraying a solution of 20 g of hydroxypropyl cellulose dissolved in 380 g of ethyl alcohol, 1,280 g of the fine powder was applied to 400 g of Nonpareil 103 (spherical sugar having a particle size of 500 to 710 μm , manufactured by Freund Industrial Co., Ltd.) to effect rolling granulation, followed by 5 hours of drying at 60°C. The resulting granules were treated with screens and those which passed through a 12 mesh screen (sieve opening, 1.41 mm) but not a 32 mesh screen (sieve opening, 0.50 mm) were collected as uncoated granules.

[0039] Next, 1,000 g of the uncoated granules thus obtained were put in a fluidized bed coating apparatus and sprayed with a coating solution composed of 8% hydroxypropylmethyl cellulose, 2% talc, 45% ethyl alcohol and 45% purified water until a 10% increase in the weight of the uncoated granules was attained. In this way, central cores of the present invention were obtained.

[0040] Thereafter, 250 g of the thus obtained central cores were put in a fluidized bed coating apparatus and sprayed with a coating solution composed of 12% Eudragit RS, 8% dimethylpolysiloxane, 4% light anhy-

drous silicic acid, 1% glycerine fatty acid ester and 75% ethyl alcohol until a 60% (Example 1-1) or 90% (Example 1-2) increase in the weight of the granules was attained. In this way, the controlled release-initiation and controlled release-rate pharmaceutical compositions of the present invention were obtained in a dosage form of granules.

COMPARATIVE EXAMPLE 1

[0041] Central cores containing trapidil were obtained in the same manner as described in Example 1.

[0042] Next, 250 g of the thus obtained central cores were put in a fluidized bed coating apparatus and sprayed with a coating solution composed of 12% Eudragit RS, 4% light anhydrous silicic acid, 1% glycerine fatty acid ester and 83% ethyl alcohol until a 60% (Comparative Example 1-1) or a 90% (Comparative Example 1-2) increase in the weight of the granules was attained. In this way, the comparative and controlled release-rate pharmaceutical compositions were obtained in a dosage form of granules.

TEST EXAMPLE 1

[0043] The inventive controlled release-initiation and controlled release-rate pharmaceutical compositions 1-1 and 1-2 obtained in Example 1 and the silicone-free comparative pharmaceutical compositions 1-1 and 1-2 obtained in Comparative Example 1 were subjected to a trapidil dissolution test in accordance with the paddle method of The Pharmacopeia of Japonica, 12th revision, using phosphate buffer (pH 6.8) as a test solution. The results are shown in Fig. 1.

[0044] As is apparent from Fig. 1, in comparison with the comparative pharmaceutical compositions 1-1 and 1-2, the controlled release-initiation and controlled release-rate pharmaceutical compositions 1-1 and 1-2 of the present invention, having the same coating ratios, are capable of releasing trapidil after a lag time.

EXAMPLE 2

[0045] The inventive controlled release-initiation and controlled release-rate pharmaceutical compositions 1-1 and 1-2 obtained as granules in Example 1 were separately packed in hard capsules in such an amount that each capsule contained 150 mg of trapidil, thereby obtaining inventive controlled release-initiation and controlled release-rate pharmaceutical compositions 2-1 and 2-2 in a dosage form of capsules.

TEST EXAMPLE 2

[0046] Each of the controlled release-initiation and controlled release-rate pharmaceutical compositions 2-1 and 2-2 of the present invention obtained in Example 2 was administered to healthy male adults in a dose of

one capsule per adult in order to measure excretion rate of trapidil into urine. The results are shown in Fig. 2.

[0047] As is apparent from Fig. 2, trapidil in the inventive controlled release-initiation and controlled release-rate pharmaceutical compositions 2-1 and 2-2 is excreted after 3 and 7 hours of lag time, respectively.

EXAMPLE 3

[0048] A 1,500 g portion of trapidil was mixed with 100 g of hydroxypropyl cellulose and pulverized into fine powder. While spraying a solution of 20 g of hydroxypropyl cellulose dissolved in 380 g of ethyl alcohol, 1,280 g of the fine powder was applied to 400 g of Nonpareil 103 (spherical sugar having a particle size of 500 to 710 μm , manufactured by Freund Industrial Co., Ltd.) to effect rolling granulation, followed by 5 hours of drying at 60°C. The resulting granules were treated with screens and those which passed through a 12 mesh screen (sieve opening, 1.41 mm) but not a 32 mesh screen (sieve opening, 0.50 mm) were collected as central cores of the present invention.

[0049] Thereafter, 250 g of the thus obtained central cores were put in a fluidized bed coating apparatus and sprayed with a coating solution composed of 6% Eudragit RS, 4% dimethylpolysiloxane, 2% light anhydrous silicic acid, 0.5% glycerine fatty acid ester and 87.5% ethyl alcohol until a 50% (Example 3-1), a 70% (Example 3-2) or a 90% (Example 3-3) increase in the weight of the granules was attained. In this way, the controlled release-initiation and controlled release-rate pharmaceutical compositions of the present invention were obtained.

TEST EXAMPLE 3

[0050] Dissolution of trapidil from the controlled release-initiation and controlled release-rate pharmaceutical compositions 3-1, 3-2 and 3-3 of the present invention obtained in Example 3 was measured in the same manner as described in Test Example 1. The results are shown in Fig. 3.

[0051] As is apparent from Fig. 3, each of the inventive pharmaceutical compositions releases trapidil quickly after a lag time, and the lag time becomes longer as the coating ratio increases. In addition, release of trapidil after lag time occurs at the same rate independent of the coating ratio.

EXAMPLE 4

[0052] Central cores containing trapidil were obtained in the same manner as described in Example 1.

[0053] Thereafter, 250 g of the thus obtained central cores were put in a fluidized bed coating apparatus and sprayed with a coating solution composed of 20% Eudragit RS, 4% dimethylpolysiloxane, 1% glycerine fatty acid ester and 75% ethyl alcohol until a 60% in-

crease in the weight of the granules was attained, thereby obtaining a controlled release-initiation and controlled release-rate pharmaceutical compositions of the present invention (Example 4-1).

[0054] In the same manner, 250 g of the thus obtained central cores were put in a fluidized bed coating apparatus and sprayed with a coating solution composed of 14% Eudragit RS, 6% dimethylpolysiloxane, 3% light anhydrous silicic acid, 2% glycerine fatty acid ester and 75% ethyl alcohol until a 70% increase in the weight of the granules was attained, thereby obtaining the controlled release-initiation and controlled release-rate pharmaceutical compositions of the present invention (Example 4-2).

[0055] Also, 250 g of the thus obtained central cores were put in a fluidized bed coating apparatus and sprayed with a coating solution composed of 10% Eudragit RS, 9% dimethylpolysiloxane, 5% light anhydrous silicic acid, 1% glycerine fatty acid ester and 75% ethyl alcohol until a 100% increase in the weight of the granules was attained, thereby obtaining the controlled release-initiation and controlled release-rate pharmaceutical compositions of the present invention (Example 4-3).

TEST EXAMPLE 4

[0056] Dissolution of trapidil from the controlled release-initiation and controlled release-rate pharmaceutical compositions 4-1, 4-2 and 4-3 of the present invention obtained in Example 4 was measured in the same manner as described in Test Example 1. The results are shown in Fig. 4.

[0057] As is apparent from Fig. 4, each of the inventive pharmaceutical compositions releases trapidil after a lag time, and the releasing rate of trapidil after the lag time can be controlled by changing the membrane composition.

EXAMPLE 5

[0058] Central cores containing trapidil were obtained in the same manner as described in Example 1.

[0059] Thereafter, 250 g of the thus obtained central cores were put in a fluidized bed coating apparatus and sprayed with a coating solution composed of 16% Eudragit RS, 4% dimethylpolysiloxane, 3% light anhydrous silicic acid, 2% glycerine fatty acid ester and 75% ethyl alcohol until a 50% (Example 5-1), an 80% (Example 5-2), a 110% (Example 5-3) or a 140% (Example 5-4) increase in the weight of the granules was attained. In this way, the controlled release-initiation and controlled release-rate pharmaceutical compositions of the present invention were obtained.

TEST EXAMPLE 5

[0060] Dissolution of trapidil from the controlled re-

lease-initiation and controlled release-rate pharmaceutical compositions 5-1, 5-2, 5-3 and 5-4 of the present invention obtained in Example 5 was measured in the same manner as described in Test Example 1. The results are shown in Fig. 5.

[0061] As is apparent from Fig. 5, each of the inventive pharmaceutical compositions releases trapidil quickly after a lag time, and the lag time becomes longer as the coating ratio increases, thus showing that the release-starting time can be changed at will.

EXAMPLE 6

[0062] Central cores containing trapidil were obtained in the same manner as described in Example 1.

[0063] Thereafter, 250 g of the thus obtained central cores were put in a fluidized bed coating apparatus and sprayed with a coating solution composed of 12% Eudragit RL, 8% dimethylpolysiloxane, 4% light anhydrous silicic acid, 1% glycerine fatty acid ester and 75% ethyl alcohol until a 60% (Example 6-1), an 80% (Example 6-2) or a 100% (Example 6-3) increase in the weight of the granules was attained. In this way, the controlled release-initiation and controlled release-rate pharmaceutical compositions of the present invention were obtained.

TEST EXAMPLE 6

[0064] Dissolution of trapidil from the controlled release-initiation and controlled release-rate pharmaceutical compositions 6-1, 6-2 and 6-3 of the present invention obtained in Example 6 was measured in the same manner as described in Test Example 1. The results are shown in Fig. 6.

[0065] As is apparent from Fig. 6, each of the inventive pharmaceutical compositions releases trapidil quickly after a lag time, and the lag time becomes longer as the coating ratio increases, thus showing that the release-starting time can be changed at will.

EXAMPLE 7

[0066] A 400 g portion of phenylpropanolamine hydrochloride was mixed with 800 g of corn starch and pulverized into fine powder. While spraying a solution of 40 g of hydroxypropyl cellulose dissolved in 760 g of ethyl alcohol, 1,280 g of the fine powder was applied to 400 g of Nonpareil 103 (spherical sugar having a particle size of 500 to 710 μ m, manufactured by Freund Industrial Co., Ltd.) to effect rolling granulation, followed by 5 hours of drying at 60°C. The resulting granules were treated with screens and those which passed through a 12 mesh screen (sieve opening, 1.41 mm) but not a 32 mesh screen (sieve opening, 0.50 mm) were collected as uncoated granules.

[0067] Next, 1,000 g of the uncoated granules thus obtained were put in a fluidized bed coating apparatus

and sprayed with a coating solution composed of 8% hydroxypropylmethyl cellulose, 2% talc, 45% ethyl alcohol and 45% purified water until a 10% increase in the weight of the uncoated granules was attained. In this way, central cores of the present invention were obtained.

[0068] Thereafter, 250 g of the thus obtained central cores were put in a fluidized bed coating apparatus and sprayed with a coating solution composed of 12% Eudragit RS, 8% dimethylpolysiloxane, 4% light anhydrous silicic acid, 1% glycerine fatty acid ester and 75% ethyl alcohol until a 40% (Example 7-1), an 80% (Example 7-2) or a 120% (Example 7-3) increase in the weight of the granules was attained. In this way, the controlled release-initiation and controlled release-rate pharmaceutical compositions of the present invention were obtained in a dosage form of granules.

TEST EXAMPLE 7

[0069] Dissolution of phenylpropanolamine hydrochloride from the controlled release-initiation and controlled release-rate pharmaceutical compositions 7-1, 7-2 and 7-3 of the present invention obtained in Example 7 was measured in the same manner as described in Test Example 1. The results are shown in Fig. 7.

[0070] As is apparent from Fig. 7, each of the inventive pharmaceutical compositions releases phenylpropanolamine hydrochloride quickly after a lag time, and the lag time becomes longer as the coating ratio increases. In addition, the release of phenylpropanolamine hydrochloride after lag time occurs at the same rate independent of the coating ratio.

EXAMPLE 8

[0071] Central cores containing trapidil were obtained in the same manner as described in Example 1.

[0072] Thereafter, 250 g of the thus obtained central cores were put in a fluidized bed coating apparatus and sprayed with a coating solution composed of 12.5% Eudragit RS, 5% dimethylpolysiloxane, 6.25% talc, 1.25% glycerine fatty acid ester and 75% ethyl alcohol until a 40% (Example 8-1) or a 65% (Example 8-2) increase in the weight of the granules was attained. In this way, the controlled release-initiation and controlled release-rate pharmaceutical compositions of the present invention were obtained in a dosage form of granules.

TEST EXAMPLE 8

[0073] Dissolution of trapidil from the controlled release-initiation and controlled release-rate pharmaceutical compositions 8-1 and 8-2 of the present invention obtained in Example 8 was measured in the same manner as described in Test Example 1. The results are shown in Fig. 8.

[0074] As is apparent from Fig. 8, each of the inven-

tive pharmaceutical compositions releases trapidil quickly after a lag time, and the lag time becomes longer as the coating ratio increases, thus showing that the release-starting time can be changed at will.

EXAMPLE 9

[0075] A 150 g portion of diclofenac sodium salt was mixed with 1,295 g of corn starch and pulverized into a fine powder. While spraying a solution of 33 g of hydroxypropyl cellulose dissolved in 627 g of ethyl alcohol, 1,051 g of the fine powder was applied to 400 g of Nonpareil 103 (spherical sugar having a particle size of 500 to 710 μm , manufactured by Freund Industrial Co., Ltd.) to effect rolling granulation, followed by 4 hours of drying at 60°C. The resulting granules were treated with screens and those which passed through a 14 mesh screen (sieve opening, 1.19 mm) but not a 32 mesh screen (sieve opening, 0.50 mm) were collected as central cores.

[0076] Thereafter, 500 g of the thus obtained central cores were put in a fluidized bed coating apparatus and sprayed with a coating solution composed of 12% Eudragit RS, 8% dimethylpolysiloxane, 4% light anhydrous silicic acid, 1% glycerine fatty acid ester and 75% ethyl alcohol until an 80% increase in the weight of the granules was attained (Example 9-1). In this way, the controlled release-initiation and controlled release-rate pharmaceutical composition 9-1 of the present invention was obtained in a dosage form of granules.

TEST EXAMPLE 9

[0077] Dissolution of trapidil from the controlled release-initiation and controlled release-rate pharmaceutical composition 9-1 of the present invention obtained in Example 9 was measured in the same manner as described in Test Example 1. The results are shown in Fig. 9.

[0078] As is apparent from Fig. 9, the inventive pharmaceutical composition releases diclofenac sodium salt after 4 hours of lag time.

EXAMPLE 10

[0079] Central cores containing trapidil were obtained in the same manner as described in Example 1.

[0080] Thereafter, 250 g of the thus obtained central cores were put in a fluidized bed coating apparatus and sprayed with a coating solution composed of 6.75% ethyl cellulose, 0.45% polyvinyl pyrrolidone, 4.8% dimethylpolysiloxane, 2.4% light anhydrous silicic acid, 0.6% glycerine fatty acid ester and 85% ethyl alcohol until a 70% increase in the weight of the granules was attained (Example 10-1). In this way, the controlled release-initiation and controlled release-rate pharmaceutical composition of the present invention was obtained in a dosage form of granules.

TEST EXAMPLE 10

[0081] Dissolution of trapidil from the controlled release-initiation and controlled release-rate pharmaceutical composition 10-1 of the present invention obtained in Example 10 was measured in the same manner as described in Test Example 1. The results are shown in Fig. 10.

[0082] As is apparent from Fig. 10, the controlled release-initiation and controlled release-rate pharmaceutical composition of the present invention releases trapidil quickly after a lag time.

EXAMPLE 11

[0083] Central cores containing trapidil were obtained in the same manner as described in Example 1.

[0084] Thereafter, 250 g of the thus obtained central cores were put in a fluidized bed coating apparatus and sprayed with a coating solution composed of 12% Eudragit S100, 8% dimethylpolysiloxane, 4% light anhydrous silicic acid, 1% glycerine fatty acid ester and 75% ethyl alcohol until a 100% increase in the weight of the granules was attained (Example 11-1). In this way, the controlled release-initiation and controlled release-rate pharmaceutical composition of the present invention was obtained in a dosage form of granules.

TEST EXAMPLE 11

[0085] Dissolution of trapidil from the controlled release-initiation and controlled release-rate pharmaceutical composition 11-1 of the present invention obtained in Example 11 was measured in the same manner as described in Test Example 1. The results are shown in Fig. 11.

[0086] As is apparent from Fig. 11, the controlled release-initiation and controlled release-rate pharmaceutical composition of the present invention releases trapidil quickly after a lag time.

EXAMPLE 12

[0087] A 900 g portion of theophylline was mixed with 100 g of talc and pulverized into fine powder. While spraying a solution of 20 g of hydroxypropyl cellulose dissolved in 380 g of ethyl alcohol, 800 g of the fine powder was applied to 200 g of Nonpareil 103 (spherical sugar having a particle size of 500 to 710 μm , manufactured by Freund Industrial Co., Ltd.) to effect rolling granulation, followed by 3 hours of drying at 60°C. The resulting granules were treated with screens and those which passed through a 14 mesh screen (sieve opening, 1.19 mm) but not a 32 mesh screen (sieve opening, 0.50 mm) were collected as central cores.

[0088] Thereafter, 400 g of the thus obtained uncoated granules were put in a fluidized bed coating apparatus and sprayed with a coating solution composed of

12% Eudragit RS, 8% dimethylpolysiloxane, 4% light anhydrous silicic acid, 1% glycerine fatty acid ester and 75% ethyl alcohol until a 25% increase in the weight of the uncoated granules was attained. In this way, the controlled release-initiation and controlled release-rate pharmaceutical composition of the present invention was obtained in a dosage form of granules.

EXAMPLE 13

[0089] A 500 g portion of pranoprofen was mixed with 500 g of microcrystalline cellulose, and the mixture was kneaded by adding 200 g of purified water, made into granules by extrusion granulation using a 0.8 mm screen and then treated with Marumerizer. After 5 hours of drying at 60°C, the resulting granules were treated with screens and those which passed through a 14 mesh screen (sieve opening, 1.19 mm) but not a 32 mesh screen (sieve opening, 0.50 mm) were collected as uncoated granules.

[0090] Thereafter, 500 g of the thus obtained uncoated granules were put in a fluidized bed coating apparatus and sprayed with a coating solution composed of 14% Eudragit RS, 7% dimethylpolysiloxane, 3% light anhydrous silicic acid, 1% glycerine fatty acid ester and 75% ethyl alcohol until a 50% increase in the weight of the uncoated granules was attained. In this way, a controlled release-initiation and controlled release-rate pharmaceutical composition of the present invention was obtained in a dosage form of granules.

EXAMPLE 14

[0091] A mixture consisting of 100 g chlorpheniramine maleate, 400 g microcrystalline cellulose, 490 g lactose and 10 g magnesium stearate was applied to a tablet machine to obtain uncoated tablets (80 mg/tablet) as central cores.

[0092] Thereafter, 500 g of the thus obtained central cores were put in a coating pan and sprayed with a coating solution composed of 7.5% Eudragit RS, 3% dimethylpolysiloxane, 1.5% light anhydrous silicic acid, 0.5% glycerine fatty acid ester and 87.5% ethyl alcohol until the weight of each tablet was increased to 10 mg. In this way, the controlled release-initiation and controlled release-rate pharmaceutical composition of the present invention was obtained in a dosage form of tablets.

COMPARATIVE EXAMPLE 2

[0093] Central cores containing trapidil were obtained in the same manner as described in Example 1.

[0094] Thereafter, 250 g of the thus obtained central cores were put in a fluidized bed coating apparatus and sprayed with a coating solution composed of 12% Eudragit RS, 4% light anhydrous silicic acid, 1% glycerine fatty acid ester, 8% corn oil and 75% ethyl alcohol until a 60% (Comparative Example 2-1) or 90% (Com-

parative Example 2-2) increase in the weight of the granules was attained. In this way, comparative pharmaceutical compositions in which silicone in the coating membrane was replaced by corn oil were obtained in a dosage form of granules.

TEST EXAMPLE 12

[0095] Dissolution of trapidil from the comparative pharmaceutical compositions 2-1 and 2-2 obtained in Comparative Example 2, in which silicone in the coating membrane was replaced by corn oil, was measured in the same manner as described in Test Example 1. The results are shown in Fig. 12, together with the results of the controlled release-initiation and controlled release-rate pharmaceutical compositions 1-1 and 1-2 of the present invention obtained in Example 1.

[0096] As is apparent from Fig. 12, the lag time prior to the commencement of drug-releasing cannot be obtained in the corn oil-applied comparative pharmaceutical compositions.

COMPARATIVE EXAMPLE 3

[0097] Central cores containing trapidil were obtained in the same manner as described in Example 1.

[0098] Thereafter, 250 g of the thus obtained central cores were put in a fluidized bed coating apparatus and sprayed with a coating solution composed of 12% Eudragit RS, 4% light anhydrous silicic acid, 1% glycerine fatty acid ester, 8% liquid paraffin and 75% ethyl alcohol until a 60% (Comparative Example 3-1) or a 90% (Comparative Example 3-2) increase in the weight of the granules was attained. In this way, comparative pharmaceutical compositions in which silicone in the coating membrane was replaced by liquid paraffin were obtained in a dosage form of granules.

TEST EXAMPLE 13

[0099] Dissolution of trapidil from the comparative pharmaceutical compositions 3-1 and 3-2 obtained in Comparative Example 3, in which silicone in the coating membrane was replaced by liquid paraffin, was measured in the same manner as described in Test Example 1. The results are shown in Fig. 13, together with the results of the controlled release-initiation and controlled release-rate pharmaceutical compositions 1-1 and 1-2 of the present invention obtained in Example 1.

[0100] As is apparent from Fig. 13, the lag time prior to the commencement of drug-releasing cannot be obtained in the liquid paraffin-applied comparative pharmaceutical compositions.

Claims

1. A controlled release-initiation and controlled re-

lease-rate pharmaceutical composition comprising a drug-containing composition coated with a membrane layer comprising

i) at least one water insoluble high polymer, and

ii) at least 5 wt.-% of a silicone, based on the weight of the component i),

the coating amount of the membrane layer is 25-200 wt.-% based on the drug-containing composition.

2. Pharmaceutical composition according to claim 1, wherein the at least one water insoluble high polymer selected from ethyl acrylate/methyl methacrylate/ethyl trimethylammonium chloride methacrylate terpolymer, ethyl cellulose, and enteric polymer.

3. Composition according to claim 2, wherein the enteric high polymer is at least one compound selected from methacrylic acid/ethyl acrylate copolymer, methacrylic acid/methyl acrylate copolymer, hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose acetate succinate, carboxymethylcellulose, and cellulose acetate succinate.

4. Composition according to any of the preceding claims, wherein the silicone is a silicone resin or a silicone oil.

5. Composition according to any of the preceding claims, wherein the membrane layer contains a silicone hold carrier.

6. Composition according to any of the preceding claims, wherein the drug-containing composition comprises a therapeutically-effective amount of a drug and a pharmaceutically acceptable carrier.

7. Composition according to any of the preceding claims, wherein the water insoluble high polymer is present in an amount of 20-95 wt.-% based on the total weight of the membrane layer, and the silicone is present in an amount of 5-200 wt.-% based on the weight of the water insoluble polymer.

8. Composition according to any of the preceding claims, wherein said membrane layer further comprises a water soluble high polymer.

9. Composition according to claim 8, wherein the water soluble high polymer is selected from hydroxypropylmethyl cellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone and polyethylene glycol.

10. Composition according to claim 2, wherein the water insoluble high polymer is ethyl acrylate/methyl methacrylate/ethyl trimethylammonium chloride methacrylate terpolymer.

11. Composition according to claim 10, wherein the terpolymer has an ethyl acrylate/methyl methacrylate/ethyl trimethylammonium chloride methacrylate weight ratio of from 1:2:0.1 to 1:2:0.2.

12. Composition according to claim 4, wherein the silicone is dimethylpolysiloxane.

13. Composition according to claim 5, wherein the silicone hold carrier is selected from talc, light anhydrous silicic acid, microcrystalline cellulose and starch.

14. Method for preparing a pharmaceutical composition according to any of the preceding claims, comprising the step of coating a drug-containing composition with a membrane-forming composition comprising a water insoluble high polymer and at least 5 wt.-% of a silicone, based on the weight of the water insoluble high polymer, in a coating amount of the membrane layer of 25-200 wt.-% based on the drug-containing composition.

15. Use of a composition comprising

i) at least one water insoluble high polymer, and

ii) at least 5 wt.-% of a silicone, based on the weight of the component i),

for coating a drug-containing composition with a membrane layer in an amount of 25-200 wt.-% based on the drug-containing composition.

Patentansprüche

1. Pharmazeutische Zusammensetzung mit gesteuerter Freisetzungsauslösung und gesteuerter Freisetzungsgeschwindigkeit, die eine wirkstoffhaltige Zusammensetzung umfasst, die mit einer Membranschicht beschichtet ist, die folgendes umfasst:

(i) mindestens ein wasserunlösliches Hochpolymer und

(ii) mindestens 5 Gew.% eines Silicons, auf Basis des Gewichts der Komponente (i),

die Beschichtungsmenge der Membranschicht beträgt 25-200 Gew.%, auf Basis der wirkstoffhaltigen Zusammensetzung.

2. Pharmazeutische Zusammensetzung gemäss Anspruch 1, worin das mindestens eine wasserunlösliche Hochpolymer ausgewählt ist aus Ethylacrylat/Methylmethacrylat/Ethyltrimethylammoniumchloridmethacrylat-Terpolymer, Ethylcellulose und enterischem Polymer. 5
3. Zusammensetzung gemäss Anspruch 2, worin das enterische Hochpolymer mindestens eine Verbindung ist, ausgewählt aus Methacrylsäure/Ethylacrylat-Copolymer, Methacrylsäure/Methylmethacrylat-Copolymer, Hydroxypropylmethylcellulosephthalat, Hydroxypropylmethylcelluloseacetatsuccinat, Carboxymethylethylcellulose und Celluloseacetatsuccinat. 10 15
4. Zusammensetzung gemäss mindestens einem der vorhergehenden Ansprüche, worin das Silicon ein Siliconharz oder ein Siliconöl ist. 20
5. Zusammensetzung gemäss mindestens einem der vorhergehenden Ansprüche, worin die Membranschicht einen Silicon-Halteträger enthält.
6. Zusammensetzung gemäss mindestens einem der vorhergehenden Ansprüche, worin die wirkstoffhaltige Zusammensetzung eine therapeutisch wirksame Menge eines Wirkstoffs und einen pharmazeutisch annehmbaren Träger umfasst. 25 30
7. Zusammensetzung gemäss mindestens einem der vorhergehenden Ansprüche, worin das wasserunlösliche Hochpolymer in einer Menge von 20-95 Gew.%, auf Basis des Gesamtgewichts der Membranschicht, vorhanden ist, und das Silicon ist in einer Menge von 5-200 Gew.%, auf Basis des Gewichts des wasserunlöslichen Polymers, vorhanden. 35
8. Zusammensetzung gemäss mindestens einem der vorhergehenden Ansprüche, worin die Membranschicht ferner ein wasserlösliches Hochpolymer umfasst. 40
9. Zusammensetzung gemäss Anspruch 8, worin das wasserlösliche Hochpolymer ausgewählt ist aus Hydroxypropylmethylcellulose, Hydroxypropylcellulose, Polyvinylpyrrolidon und Polyethylenglykol. 45
10. Zusammensetzung gemäss Anspruch 2, worin das wasserunlösliche Hochpolymer Ethylacrylat/Methylmethacrylat/Ethyltrimethylammoniumchloridmethacrylat-Terpolymer ist. 50
11. Zusammensetzung gemäss Anspruch 10, worin das Terpolymer ein Ethylacrylat/Methylmethacrylat/Ethyltrimethylammoniumchloridmethacrylat-Gewichtsverhältnis von 1:2:0,1 bis 1:2:0,2 aufweist. 55
12. Zusammensetzung gemäss Anspruch 4, worin das Silicon Dimethylpolysiloxan ist.
13. Zusammensetzung gemäss Anspruch 5, worin der Silicon-Halteträger ausgewählt ist aus Talk, leichter wasserfreier Kieselsäure, mikrokristalliner Cellulose und Stärke.
14. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung gemäss mindestens einem der vorhergehenden Ansprüche, das den Schritt der Beschichtung einer wirkstoffhaltigen Zusammensetzung mit einer membranbildenden Zusammensetzung, die ein wasserunlösliches Hochpolymer und mindestens 5 Gew.% eines Silicons, auf Basis des Gewichts des wasserunlöslichen Hochpolymers, in einer Beschichtungs Menge der Membranschicht von 25-200 Gew.%, auf Basis der wirkstoffhaltigen Zusammensetzung, umfasst.
15. Verwendung einer Zusammensetzung, die
 - (i) mindestens ein wasserunlösliches Hochpolymer und
 - (ii) mindestens 5 Gew.% eines Silicons auf Basis des Gewichts der Komponente (i), umfasst,
 zur Beschichtung einer wirkstoffhaltigen Zusammensetzung mit einer Membran in einer Menge von 25-200 Gew.%, auf Basis der wirkstoffhaltigen Zusammensetzung.

Revendications

1. Composition pharmaceutique avec commencement et vitesse contrôlés de la libération comprenant une composition contenant un médicament, revêtue d'une membrane pelliculaire comprenant
 - i) au moins un haut-polymère insoluble dans l'eau et
 - ii) au moins 5 % en poids d'une silicone, sur la base du poids du composant i),
 la quantité de revêtement de la membrane pelliculaire étant de 25 à 200 % en poids sur la base de la composition contenant le médicament.
2. Composition pharmaceutique selon la revendication 1, dans laquelle au moins l'un des haut-polymères insoluble dans l'eau est sélectionné à partir d'un terpolymère acrylate d'éthyle/ méthacrylate de méthyle/méthacrylate de chlorure de triméthylammonium éthyle, d'éthyle cellulose et de polymère entérique.

3. Composition selon la revendication 2, dans laquelle le haut-polymère entérique est au moins un composé sélectionné à partir de copolymère d'acide méthacrylique/ acrylate d'éthyle, de copolymère d'acide méthacrylique/ méthacrylate de méthyle, d'hydroxypropylméthylcellulose phtalate, d'hydroxypropylméthylcellulose acétate succinate, de carboxyméthyléthyl cellulose et de succinate d'acétate de cellulose. 5
4. Composition selon l'une quelconque des revendications précédentes, dans laquelle la silicone est une résine de silicone ou une huile de silicone. 10
5. Composition selon l'une quelconque des revendications précédentes, dans laquelle la membrane pelliculaire contient un support de silicone. 15
6. Composition selon l'une quelconque des revendications précédentes, dans laquelle la composition contenant un médicament comprend une quantité efficace sur le plan thérapeutique d'un médicament et un support acceptable sur le plan pharmaceutique. 20
7. Composition selon l'une quelconque des revendications précédentes, dans laquelle le haut-polymère insoluble dans l'eau est présent en une quantité de 20 à 95 % en poids sur la base du poids total de la membrane pelliculaire, et la silicone est présente en une quantité de 5 à 200 % en poids sur la base du poids du polymère insoluble dans l'eau. 25
8. Composition selon l'une quelconque des revendications précédentes, dans laquelle ladite membrane pelliculaire comprend un haut-polymère soluble dans l'eau. 30
9. Composition selon la revendication 8, dans laquelle le haut-polymère soluble dans l'eau est sélectionné à partir d'hydroxypropylméthyl cellulose, d'hydroxypropyl cellulose, de polyvinyle pyrrolidone et de polyéthylène glycol. 35
10. Composition selon la revendication 2, dans laquelle le haut-polymère insoluble dans l'eau est le terpolymère éthyle acrylate/méthyle méthacrylate/méthacrylate de chlorure de triméthylammonium éthyle. 40
11. Composition selon la revendication 10, dans laquelle le terpolymère présente un rapport de l'éthyle acrylate/méthyle méthacrylate/méthacrylate de chlorure de triméthylammonium éthyle allant de 1 : 2 : 0,1 à 1 : 2 : 0,2. 45
12. Composition selon la revendication 4, dans laquelle la silicone est de la diméthylpolysiloxane. 50
13. Composition selon la revendication 5, dans laquelle le support de silicone est sélectionné à partir de talc, d'acide silicique anhydre léger, de cellulose microcristalline et d'amidon. 55
14. Procédé de préparation d'une composition pharmaceutique selon l'une quelconque des revendications précédentes, comprenant l'étape consistant à revêtir la composition contenant le médicament d'une composition formant une membrane, comprenant un haut-polymère insoluble dans l'eau et au moins 5 % en poids d'une silicone sur la base du poids du haut-polymère insoluble dans l'eau, en une quantité de revêtement de la membrane pelliculaire de 25 à 200 % en poids sur la base de la composition contenant le médicament.
15. Utilisation de la composition, comprenant
 - i) au moins un haut polymère insoluble dans l'eau et
 - ii) au moins 5 % en poids d'une silicone, sur la base du poids du composant i),
 pour revêtir une composition contenant un médicament avec une membrane pelliculaire en une quantité de 25 à 200 % en poids sur la base de la composition contenant le médicament.

Fig. 1

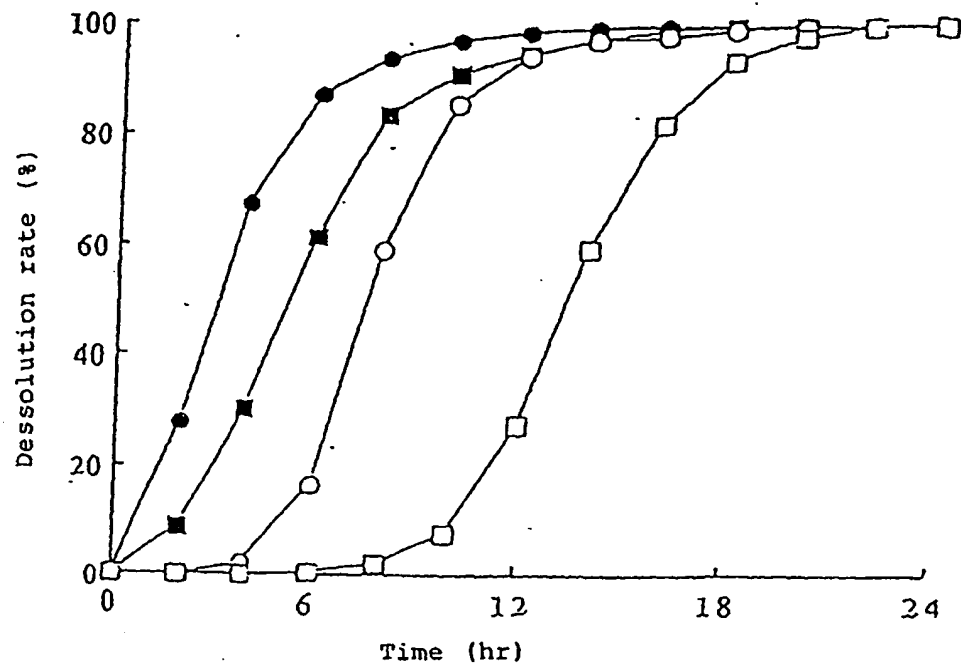


Fig. 2

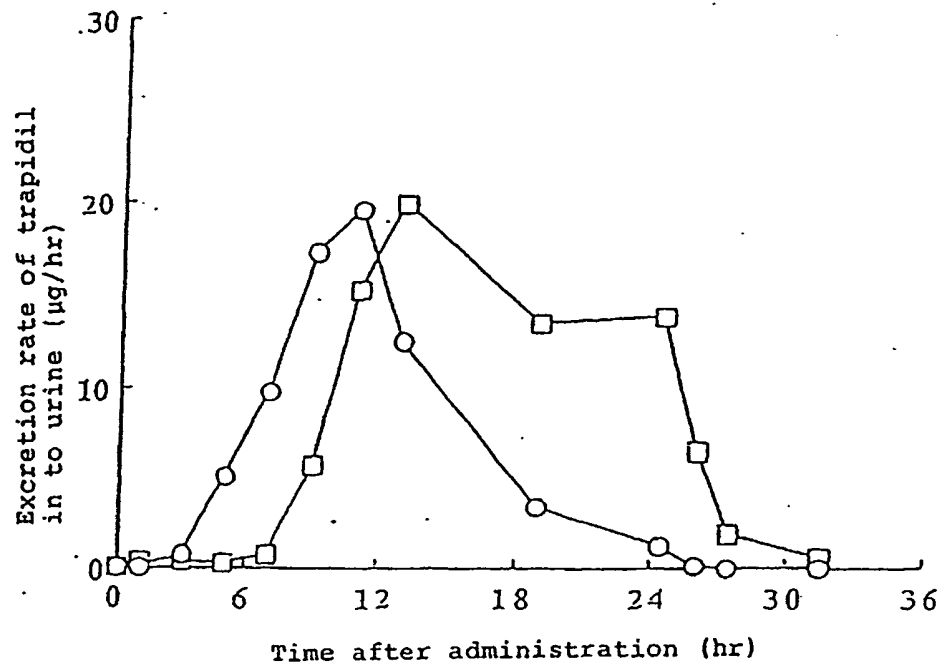


Fig. 3

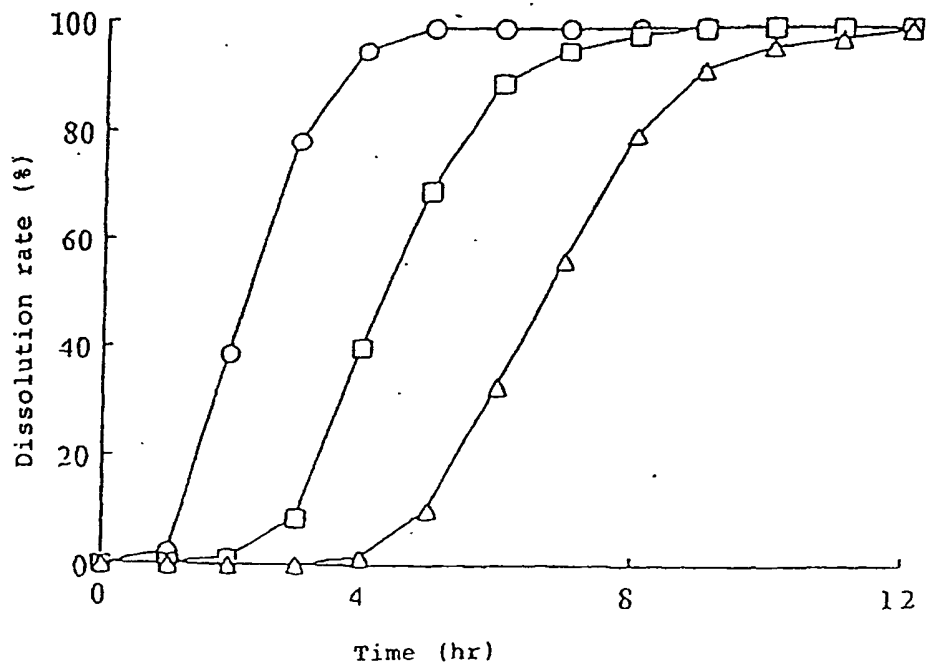


Fig. 4

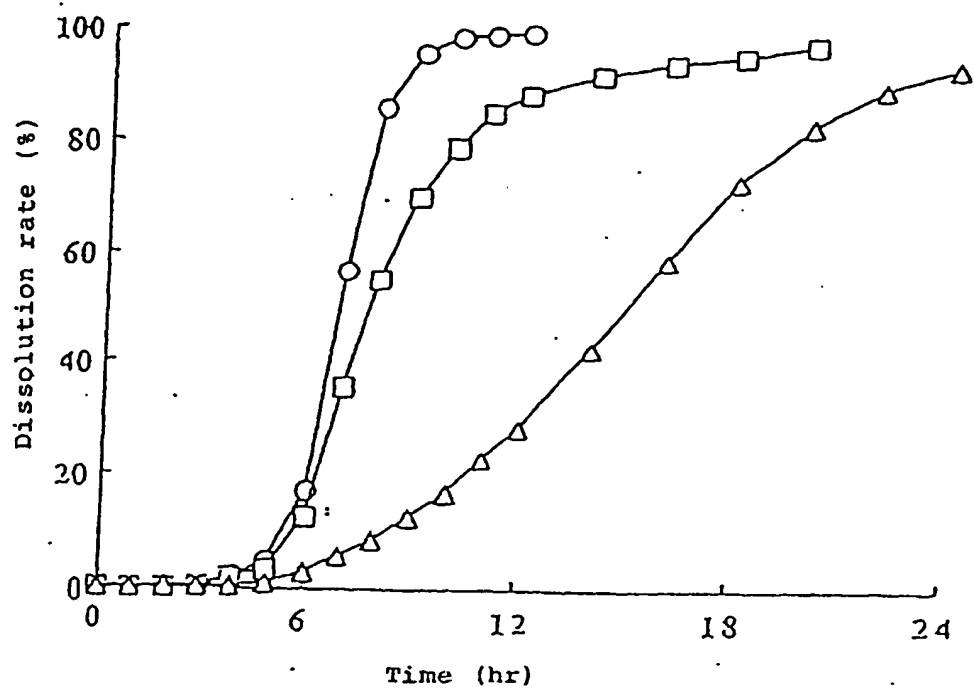


Fig. 5

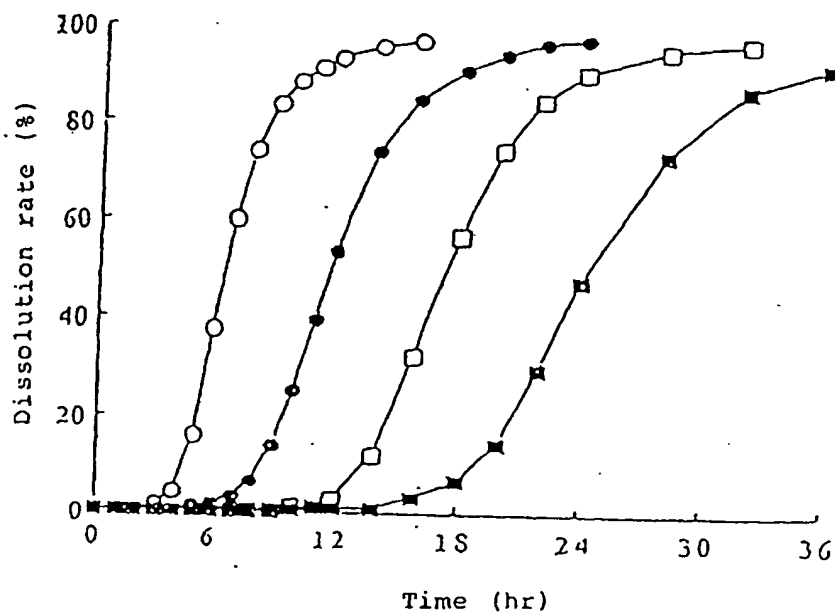


Fig. 6

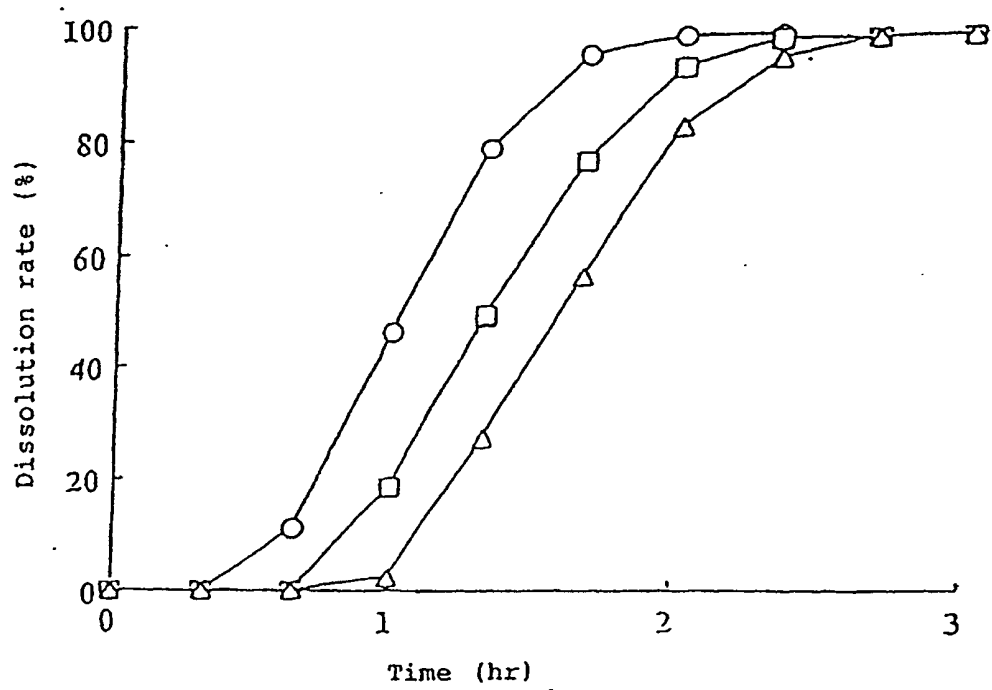


Fig. 7

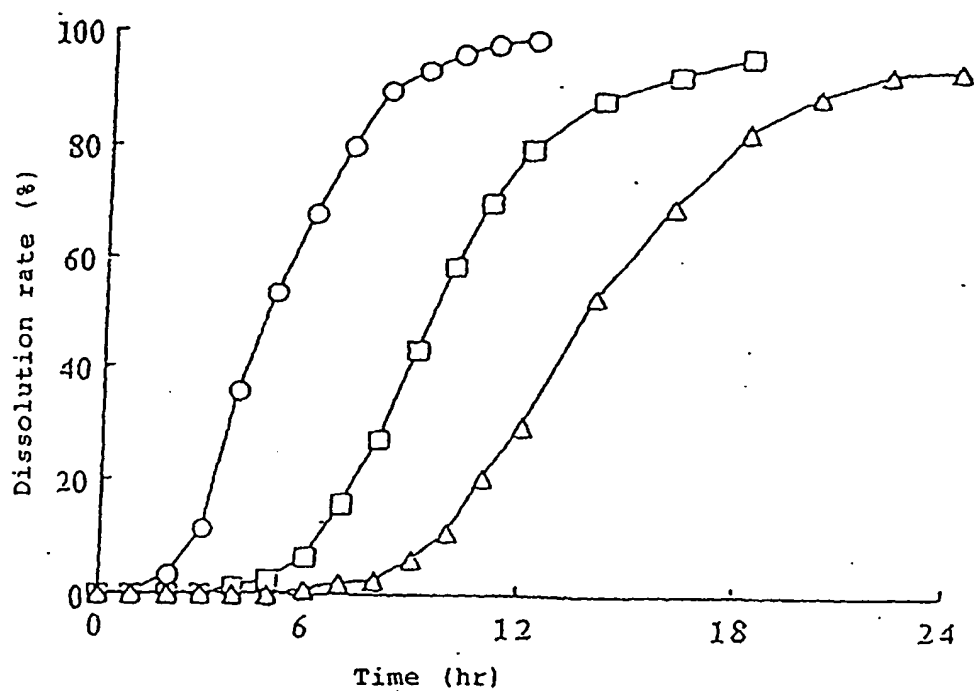


Fig. 8

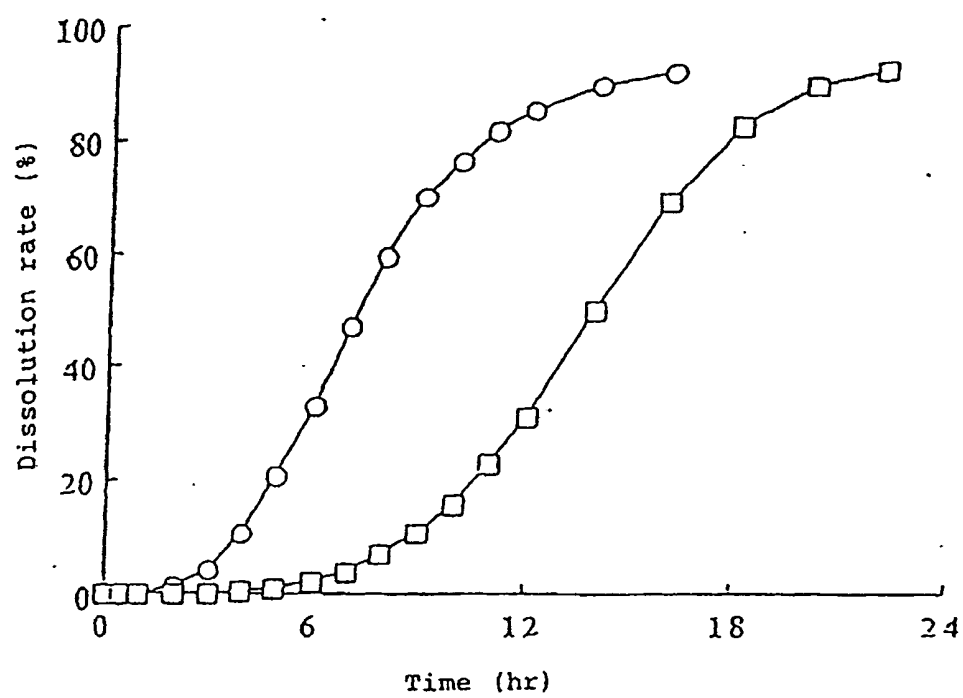


Fig. 9

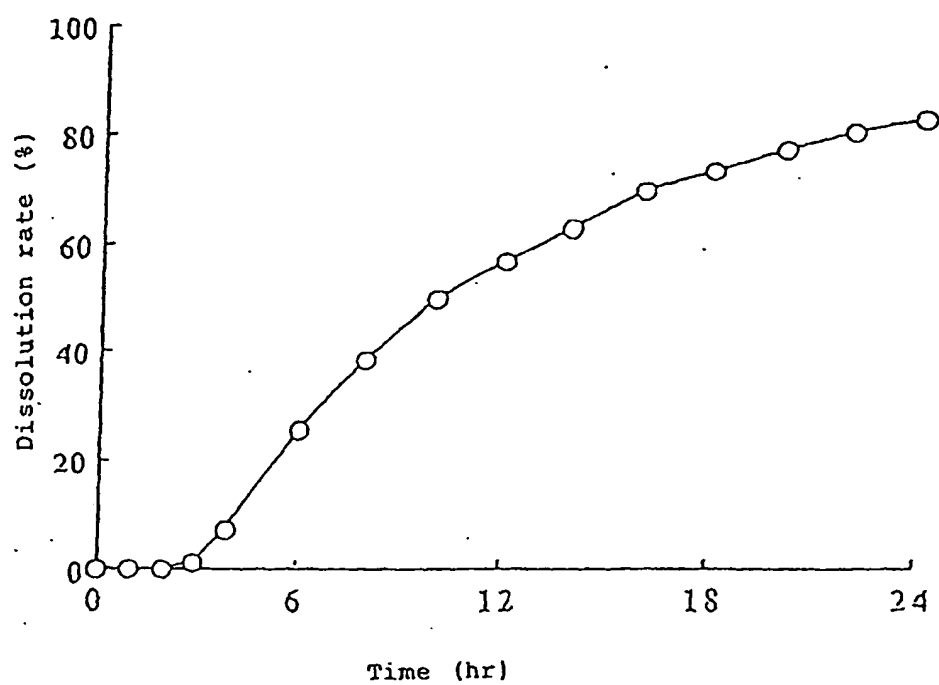


Fig. 10

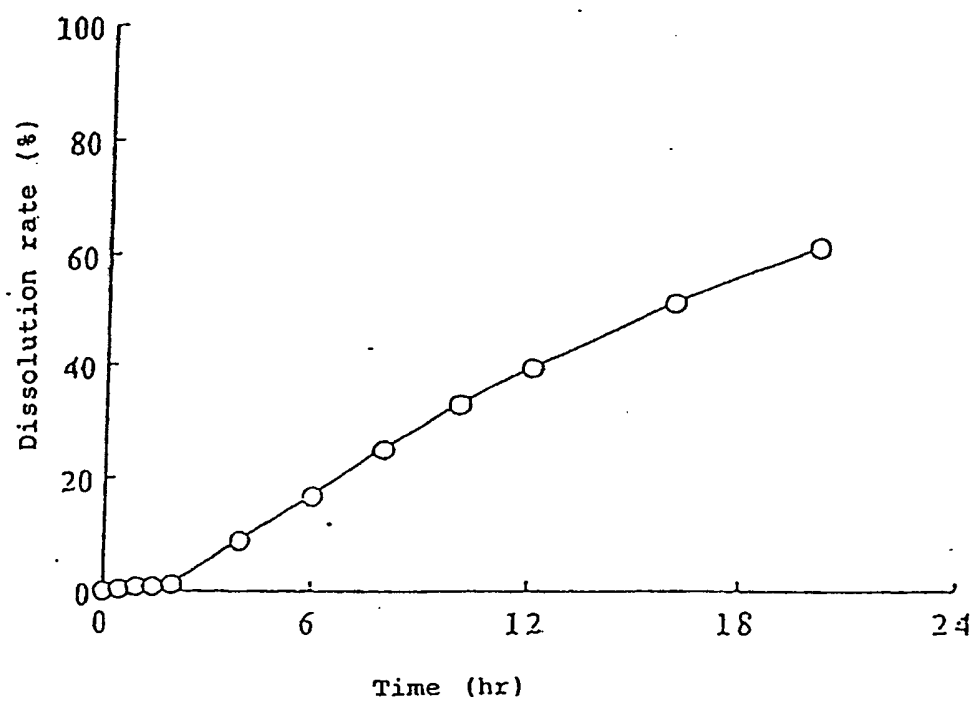


Fig. 11

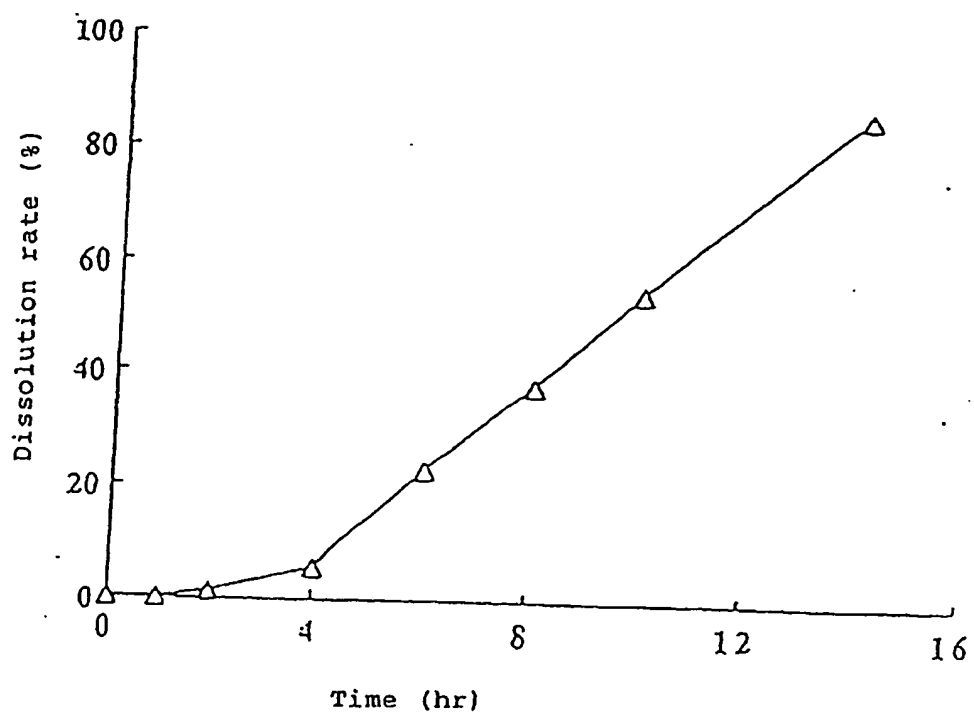


Fig. 12

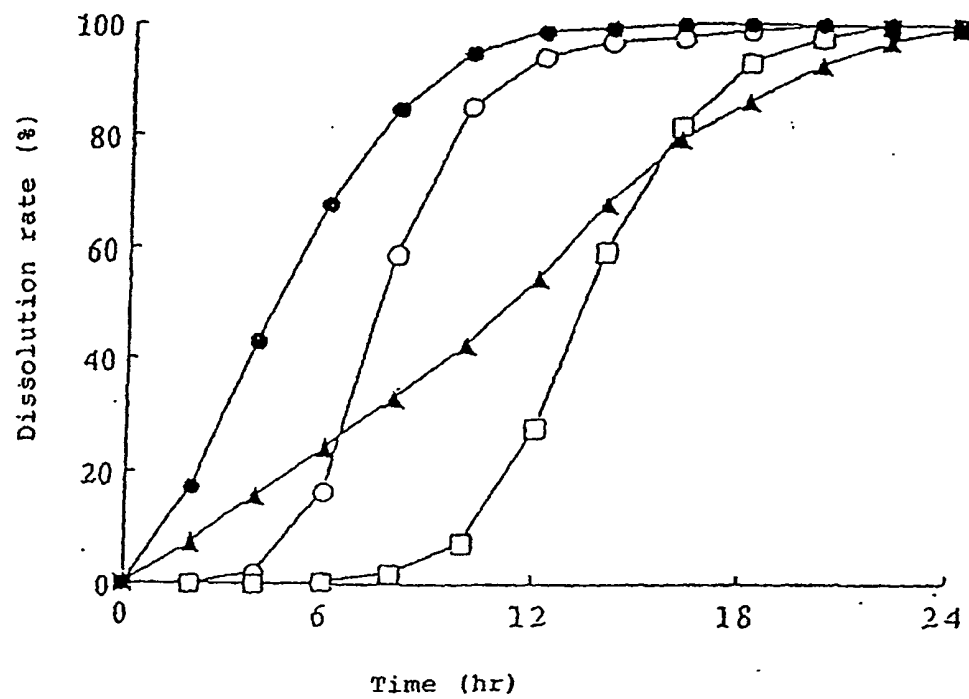
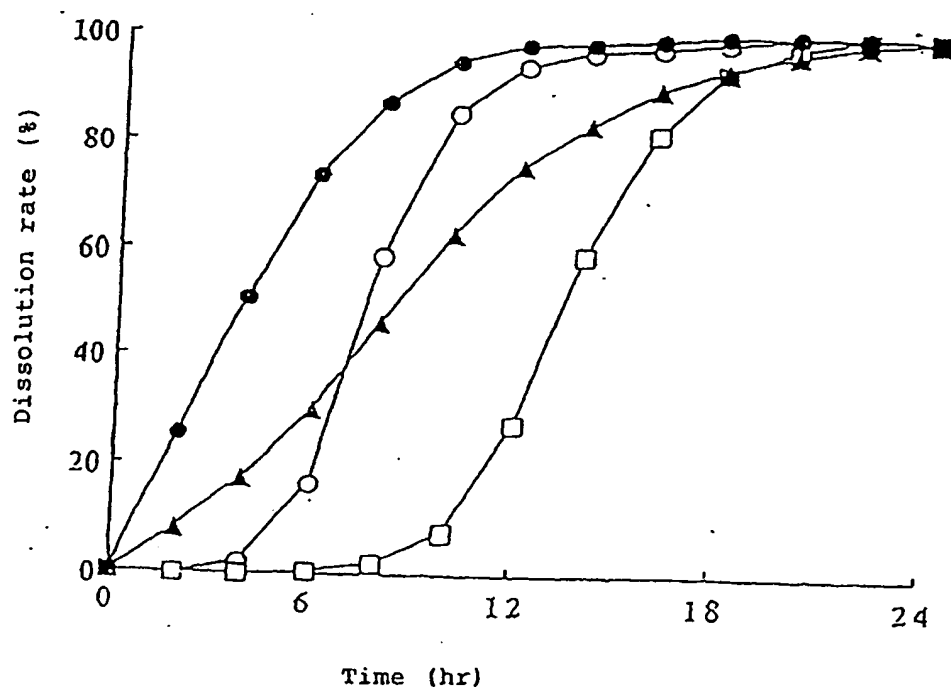


Fig. 13



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